523. *The Reactions of Organic Phosphates. Part V.** *The Hydrolysis of Triphenyl and Trimethyl Phosphates.*

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In neutral or acidic solution trimethyl phosphate undergoes hydrolysis with carbon–oxygen bond fission, and acid-catalysis is not observed. The second-order reaction with hydroxide ions, on the other hand, proceeds with phosphorus–oxygen bond fission. Similarly triphenyl phosphate is hydrolysed with phosphorus–oxygen bond fission in alkaline solution. The latter reaction, which has a low activation energy (*ca.* 10 kcal. mole^{-1}), has been shown not to involve isotopic exchange at the phosphoryl oxygen atom.

Simple trisubstituted phosphate esters are known to be relatively alkali-labile:[1-3] with the exception of an investigation of trimethyl phosphate by Hudson and Harper,[4] however,

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* Part IV, *J.*, 1961, 1636.

[1] Cavalier, *Compt. rend.*, 1898, **127**, 60.

[2] Plimmer and Burch, *J.*, 1929, 279.

[3] Bailly and Gaumé, *Bull. Soc. chim. France*, 1936, **53**, 1396.

[4] Hudson and Harper, *J.*, 1958, 1356.

little kinetic work has been reported. Blumenthal and Herbert[5] found that alkaline hydrolysis of trimethyl phosphate proceeds with phosphorus–oxygen bond fission. Their result for hydrolysis in acid solution (*ca.* 70% carbon–oxygen bond fission) is less informative since (*a*) the use of hydrochloric acid introduced complexities due to the possible formation of methyl chloride,[6] (*b*) secondary hydrolysis of the product, dimethyl phosphate, occurred under the experimental conditions, and (*c*) the rôle of acid-catalysed processes was not elucidated.

In this paper the results are presented of a kinetic and isotopic study of the hydrolyses of trimethyl and triphenyl phosphates. Preliminary accounts of our work have already appeared.[7, 8]

EXPERIMENTAL

Materials.—A commercial sample of trimethyl phosphate was fractionated; it had b. p. 74·1—74·5°/10·5 mm., $n_D^{24\cdot7}$ 1·3922 (Found: C, 25·1; H, 6·9; P, 22·3. Calc. for $C_3H_9O_4P$: C, 25·7; H, 6·5; P, 22·2%). Commercial triphenyl phosphate was recrystallised three times from ethanol and had m. p. 49°. Diphenyl hydrogen phosphate was prepared from phenol and phosphorus oxychloride and had m. p. 68°. Dioxan was purified as described by Vogel.[9]

TABLE 1. *Hydrolysis of trimethyl phosphate (TMP) in aqueous alkali.*

T	[NaOH], M	[TMP], M	10^3k_2	T	[NaOH], M	[TMP], M	10^3k_2
35·0°	0·334	0·242	0·330	65·5°	0·122	0·062	3·35
35·0	0·313	0·0645	0·338	69·3	0·143	0·086	4·78
35·0	0·164	0·0667	0·340	73·0	0·123	0·060	5·90
35·0	0·0770	0·0619	0·335	35·0 *	0·0210	0·0234	0·247
44·7	0·346	0·248	0·748				

* In dioxan–water (75 : 25 v/v).

Kinetic Measurements.—(1) *Trimethyl phosphate in alkaline solution.* The sealed-tube technique was used. The tubes were opened under excess of acid, and the resulting solutions titrated with standard base, Methyl Red–Methylene Blue being used as indicator. The reactions did not proceed beyond the removal of one methyl group. This is consistent with the known resistance of dimethyl phosphate to alkaline hydrolysis.[10, 11] Good second-order rate coefficients were obtained in each run. The results are shown in Table 1; k_2 has the units l. mole^{-1} sec.$^{-1}$.

Variations in the concentrations of the substrate are without effect on k_2. Change of solvent to dioxan–water (3 : 1 v/v) produces a small decrease in rate. The Arrhenius parameters (E and A), calculated from the data over the range 35·0—73·0°, are 16·2 kcal. mole^{-1} and $10^{8\cdot1}$ l. mole^{-1} sec.$^{-1}$, respectively.

(2) *Trimethyl phosphate in neutral and acidic solutions.* The reactions were followed by titration with standard base, Methyl Red–Methylene Blue being used as indicator, of the dimethyl phosphate produced. Because dimethyl phosphate is also hydrolysed in acidic solution, theoretical infinity values corresponding to the removal of one methyl group were used in the calculation of first-order rate coefficients, and the reactions were followed only to *ca.* 20% of reaction. With 0·2M-perchloric acid at 100° the first-order rate coefficient for the hydrolysis of trimethyl phosphate measured in this way was found to be $0\cdot373 \times 10^{-4}$ sec.$^{-1}$. Under the same conditions the corresponding value for dimethyl phosphate[10] is $0\cdot393 \times 10^{-5}$ sec.$^{-1}$. Calculation shows that, over the first 20% of the hydrolysis of trimethyl phosphate, disturbance due to secondary hydrolysis of the product is negligible.

A different procedure was necessary for experiments in which a relatively large amount of perchloric acid was initially present. Aliquot portions, after removal from a thermostat-bath, were exactly neutralised with sodium hydroxide, and a known excess of standard sodium

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[5] Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611.

[6] Cherbuliez and Leber, *Helv. Chim. Acta*, 1952, **35**, 2539.

[7] Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.

[8] Vernon, *Chem. Soc. Spec. Publ.*, 1957, No. 8, 17.

[9] Vogel, " Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 177.

[10] Bunton, Mhala, Oldham, and Vernon, *J.*, 1960, 3293.

[11] Kumamoto, Cox, and Westheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 4858.

hydroxide was then added. Titration with standard acid, after heating until all the trimethyl phosphate had hydrolysed, enabled the concentration of trimethyl phosphate remaining in the original experiment at any time, *t*, to be calculated. The precision of the rate coefficients obtained by this procedure was *ca.* ±10%.

Table 2 summarises the results obtained.

TABLE 2. *The hydrolysis of trimethyl phosphate* (ca. 0·25M) *in neutral and acid solutions.*

T	$[HClO_4]$ (M)	10^5k	T	$[HClO_4]$ (M)	10^5k_1
44·7°	—	0·016	100·1°	—	3·65
65·5	—	0·158	100·1	0·10	3·83
73·0	—	0·330	100·1	0·20	4·05
80·0	—	0·658	100·1	3·0	4·33

The Arrhenius parameters (E and A) for the solvolytic reaction are 22·7 kcal. mole^{-1} and $10^{8·9}$ l. mole^{-1} sec.$^{-1}$, respectively.

(3) *Triphenyl phosphate in alkaline solution.* The rate of reaction with alkali in aqueous dioxan was followed by estimation of the phenol produced, by using the reagent introduced by Folin and Ciocalteu.[12] The following details of a run with 0·00624M-triphenyl phosphate and 0·0182M-sodium hydroxide in dioxan–water (3 : 2 v/v) at 10·1°, are typical. Dioxan (17·6 ml.), 60% dioxan–water (10 ml.), and dioxan containing 4·181 g. of triphenyl phosphate per 100 ml. (5·03 ml.) were mixed in a flask, which was placed in a thermostat bath at 10·1° and allowed to come to thermal equilibrium. Carbonate-free sodium hydroxide solution (0·1228N; 15·0 ml.) at 10·1° was then added, and the mixture made up to 100 ml. with 60% dioxan–water at 10·1°. Aliquot portions (10 ml.) were removed at appropriate time intervals and pipetted into flasks containing 0·12M-perchloric acid (5 ml.). Water (50 ml.) and Folin's reagent (5 ml.) were added, in the order stated, and the volume was made up to 100-ml. with water. After 80 min. the solutions were centrifuged at 3000**g** for 20 min. to remove precipitated triphenyl phosphate. Colour intensities were then measured in a Spekker photoelectric absorptiometer, a red filter being used. The contents of phenol were then determined by reference to a standard curve.

t (min.)	0	1·33	2·41	4·00	5·33	7·33
Phenol (mg./sample)	0·179	0·222	0·258	0·303	0·335	0·394
10^2k_2, l. mole^{-1} sec.$^{-1}$	—	0·507	0·532	0·485	0·467	0·467

Diphenyl phosphate undergoes slow hydrolysis in alkaline solution but the rate is too small to interfere with this procedure.

A few rates were measured by a simple acid–base titration method (*e.g.*, as described for trimethyl phosphate). Since, in this case, both products (*i.e.*, phenol and diphenyl phosphate) are acidic, second-order rate coefficients were calculated from the equation,

$$k_2 = \frac{2·303}{t(2a - b)} \log_{10} \frac{b(a - x)}{a(b - 2x)}$$

where a and b are the initial concentrations of sodium hydroxide and triphenyl phosphate, respectively. In dioxan–water (3 : 1 v/v) at 35·0°, the mean values of k_2 were 0·0253 and 0·0227 l. mole^{-1} sec.$^{-1}$ for the colorimetric and acid–base method, respectively. In 60% dioxan–water the mean values of 10^2k_2 (l. mole^{-1} sec.$^{-1}$) at 0°, 10·1°, 24·7°, and 35·0° were 0·235, 0·477, 1·06, and 2·32, respectively. Hence $E = 10·2$ kcal. mole^{-1} and $A = 10^{4·9}$ l. mole^{-1} sec.$^{-1}$.

The solvolytic reaction was too slow for accurate measurement. The mean value of the first-order rate coefficient (100·1°) was $6·0 \pm 0·1 \times 10^{-8}$ sec.$^{-1}$.

(4) *Isotope experiments.* The hydrolysis of trimethyl phosphate was carried out under a variety of conditions in water enriched in oxygen-18. The concentrations of trimethyl phosphate were usually in the range 1·5—2·5M and the volumes of solutions were so chosen that *ca.* 3 ml. of pure methanol were finally recovered. Methanol was isolated and isotopically analysed as previously described.[13] The results are shown in Table 3, where N_s and N_m are the atom-percentages excess abundance of oxygen-18 in the solvent and in the isolated methanol,

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[12] Folin and Ciocalteu, *J. Biol. Chem.*, 1927, **73**, 627.

[13] Bunton, Llewellyn, Oldham, and Vernon, *J.*, 1958, 3574.

respectively, and Q_c the proportion of the reaction proceeding with carbon–oxygen bond fission. Q_c is given simply by N_m/N_s since, under all the relevant conditions, the oxygen exchange of methanol is negligibly slow.[13]

The results show that, within the experimental error, the reaction in alkaline solution proceeds entirely with phosphorus–oxygen bond fission. Similarly in initially neutral or acidic solutions the reaction proceeds entirely with carbon–oxygen bond fission. For the reason already given, no ambiguity is introduced into these results by secondary hydrolysis of dimethyl phosphate. The experiment in which an attempt was made to keep the solution exactly neutral by addition of sodium hydroxide gave a result indicating the occurrence of both kinds of bond fission. Since the reaction with hydroxide ions is so much faster than the solvolysis, this presumably arises from local concentrations of sodium hydroxide in the addition process and has no mechanistic significance.

TABLE 3. *Isotope results: hydrolysis of trimethyl phosphate.*

Conditions	N_s	N_m	Q_c
3·44M-NaOH, 35°, complete reaction	0·423	0·014	0·03
0·62M-NaOH, 35°, complete reaction	0·957	0·002, 0·035	0·00, 0·04
Neutral (to Methyl Red) by addition of NaOH, 100°, 25% reaction	0·911	0·540	0·59
1·0M-HClO$_4$, 100° 28% reaction	0·647	0·616	0·95
0·1M-HClO$_4$, 100°, 28% reaction	0·337	0·341	1·01
Initially neutral, 28% reaction	0·647	0·647, 0·642	1·00, 0·99

The position of bond fission in the reaction of triphenyl phosphate and hydroxide ions was also determined. A solution (250 ml.) of triphenyl phosphate (0·025M) and sodium hydroxide (0·1M) in 75% dioxan-water containing 0·65% excess abundance of oxygen-18 in the water, was placed in a thermostat-bath at 35°. Phenol was extracted, distilled at 3 mm., and then pyrolysed to carbon monoxide, which was analysed mass-spectrometrically. The result showed that the isolated phenol contained $-0{\cdot}00_3$% excess abundance of oxygen-18. The reaction proceeds, therefore, with phosphorus–oxygen bond fission.

Experiments designed to detect oxygen exchange at the phosphoryl oxygen were carried out on both triphenyl and trimethyl phosphate. The procedures used depended on the amount of enriched water available. The following details are illustrative; (*A*) A solution (250 ml.) of triphenyl phosphate (*ca.* 0·02M) and sodium hydroxide (*ca.* 0·025M) in dioxan–water (3 : 1 v/v), containing excess abundance (*ca.* 1·0%) of oxygen-18 in the water, was allowed to react at 25° for 3·5 min. (*ca.* 43% reaction). Addition of excess of 0·1M-hydrochloric acid stopped the reaction. The mixture was extracted several times with petroleum. The combined extracts were washed (water), dried, and evaporated. The resulting solid was dried *in vacuo* over phosphoric oxide, and then had m. p. and mixed m. p. 46·5—48°. (*B*) Water (0·5 ml.) containing a large excess abundance of oxygen-18 (*ca.* 30%) was slowly added to a mixture of dioxan (3 ml.) and sodium (0·2 g.). Triphenyl phosphate (1·3 g.) was then added and the mixture was shaken for 5 min. at 25°. The extraction and isolation of triphenyl phosphate were then carried out as above.

Two methods were used for the determination of the isotopic abundance of the unchanged triphenyl phosphate.

(1) The phosphate was heated with mercuric chloride for 3 hr. at 525° *in vacuo* (Rittenberg and Ponticorvo's method [14]). The carbon dioxide so obtained was contaminated with volatile impurities which interfered with the mass-spectrometric analysis. These impurities were removed by passing the gas through a column (2 ft.) packed with silicone oil on Celite and maintained at −80°. This method of decomposition should eliminate all four of the oxygen atoms of triphenyl phosphate, although some differentiation between the phosphoryl oxygen and the three ester oxygen atoms may occur.

(2) A known weight of triphenyl phosphate was heated with *o*-phenylenediamine hydrochloride in the presence of a known amount of carbon dioxide at 325° for 3 hr. (Dahn, Moll, and Menassé's method [15]). A control experiment with isotopically normal triphenyl phosphate and $C^{18}O_2$ showed that *ca.* 60% exchange occurred under the experimental conditions. The method is, therefore, satisfactory for the qualitative detection of isotopic labelling in the phosphoryl oxygen atom. The three ester oxygen atoms will not be affected by this procedure.[15]

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[14] Rittenberg and Ponticorvo, *Int. J. Appl. Rad. Isot.*, 1956, **1**, 208.

[15] Dahn, Moll, and Menassé, *Helv. Chim. Acta*, 1959, **52**, 1226.

Table 4 gives the results obtained: N_s and N_p refer to the excess abundance of oxygen-18 in the water and in the unchanged phosphate, respectively.

TABLE 4. *Isotopic composition of phosphates isolated from partial hydrolysis.*

Substrate	N_s (%)	N_p (%)	Analysis *
Triphenyl phosphate	1·44	$0{\cdot}01_2$	D
„	1·33	$0{\cdot}00_5$	R
„	33	$0{\cdot}01_5$	R
Trimethyl phosphate	1·44	0·01	R

* D, Dahn, Moll, and Menassé's method [15]; R, Rittenberg and Ponticorvo's method.[14]

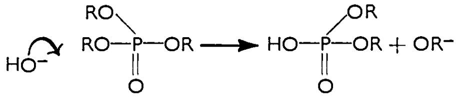
The small amount of enrichment actually observed probably arises from incomplete removal of impurities (*e.g.*, Me_2O, mass number 46). It is significant that the observed enrichment with triphenyl phosphate is no greater with water enriched by *ca.* 30% than with water enriched by *ca.* 1%. The isotope results indicate, therefore, that the hydrolytic reactions of triphenyl and trimethyl phosphate are not associated with appreciable isotopic exchange at the phosphoryl oxygen atoms.

The infrared spectrum of a solution (in carbon tetrachloride) of the triphenyl phosphate isolated from partial hydrolysis in the solvent containing heavily enriched water (33% excess abundance of oxygen-18) was compared, a Grubb-Parsons double-beam infrared spectrometer being used, with the spectrum of a solution (in carbon tetrachloride) of the initial material. The spectra were identical: in particular, the peaks of the doublet assigned to the P=O stretching [16] were at 1299 and 1314 cm.$^{-1}$ and 1301 and 1315 cm.$^{-1}$ for the initial and recovered samples, respectively. It is known [17] that the stretching frequency of the P=O group moves to lower frequencies (by *ca.* 30 cm.$^{-1}$) upon substitution of oxygen-16 for oxygen-18. Although this method is not sufficiently sensitive to detect a small isotopic enrichment, the result shows that no large isotopic exchange remains undetected by the other analytical methods.

DISCUSSION

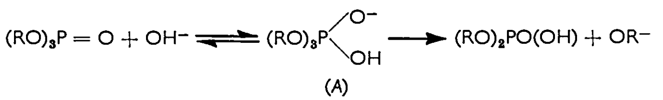
The reactions of trimethyl and triphenyl phosphate with hydroxide ions proceed with phosphorus–oxygen bond fission. The rates of the reactions are not much affected by solvent changes. For example, with trimethyl phosphate change of solvent from water to dioxan–water (3 : 1 v/v) reduces the rate by only *ca.* 25%. Triphenyl phosphate is, within the experimentally accessible range, the more reactive compound: at 35° in 75% dioxan–water, the rate factor is *ca.* 100. It would appear, therefore, that a correlation exists between rate and stability (as judged by the p*K* of the conjugate acid) of the displaced anion. However, in this case simple rate comparisons are ambiguous. Calculation shows that at 113·4°, the order of reactivity is reversed. It is probably better, therefore, to correlate the activation energy with the stability of the displaced anion.

These facts are consistent with the formulation of the reaction as a simple nucleophilic displacement (*i.e.*, of the S_N2 type) at the phosphorus atom:



$$HO^- + (RO)_3P{=}O \longrightarrow HO{-}P(O)(OR)_2 + OR^- \quad . . . . (1)$$

However, for triphenyl phosphate the observed activation energy (10·2 kcal. mole^{-1}) is abnormally low for a reaction involving a negatively charged nucleophile and a neutral molecule. It seemed possible, therefore, that at least with triphenyl phosphate, hydrolysis involves an intermediate adduct (*A*):



$$(RO)_3P=O + OH^- \rightleftharpoons (RO)_3P\begin{smallmatrix}O^-\\OH\end{smallmatrix} \longrightarrow (RO)_2PO(OH) + OR^- \quad . . . . (2)$$

(*A*)

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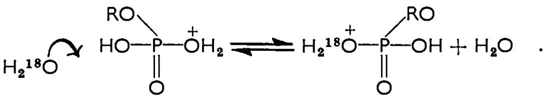
[16] Bellamy and Beecher, *J.*, 1952, 475.

[17] Holmann and Pinchas, *Bull. Res. Council Israel*, 1958, **7***A*, 101.

In the sequence (2), if the formation of (*A*) is relatively fast and reversible, and if all the steps are slower than proton transfers involving the OH and O^- groups of intermediate *A*, then hydrolysis will be associated with isotopic exchange at the phosphoryl oxygen atom. Experiments designed to test this were carried out both with triphenyl and trimethyl phosphate. No exchange at the phosphoryl oxygen atom has been detected with either compound. It appears, therefore, that the reactions of trisubstituted phosphates with hydroxide ion must be formulated as in scheme (1), *i.e.*, as S_N2 processes at a phosphorus centre.

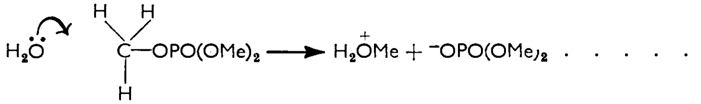
Holmann [18] has reported that the hydrolysis of di-isopropyl phosphorofluoridate is also not accompanied by isotope exchange at the phosphoryl oxygen atom. Oxygen-exchange reactions (although not necessarily involving the phosphoryl oxygen) have been observed only with phosphate mono- and di-esters in acid solution.[13,19] The evidence suggests, therefore, that quinquecovalent adducts of type (*A*) are never formed during the hydrolysis of phosphate esters, and that the exchange reactions observed in acid solution are simple S_N2 displacements of water by water, *i.e.*,



$$H_2{}^{18}O\ \ HO{-}\overset{\displaystyle RO}{\underset{\displaystyle O}{P}}{-}\overset{+}{O}H_2 \rightleftharpoons H_2{}^{18}\overset{+}{O}{-}\overset{\displaystyle RO}{\underset{\displaystyle O}{P}}{-}OH + H_2O \quad . \ . \ . \ . \ . \ . \ . \quad (3)$$

The results with triphenyl phosphate make it possible to compare the nucleophilic powers of water and hydroxide ions towards phosphorus.* The specific second-order rate coefficients at 100° in dioxan–water (3 : 2 v/v) are approximately 3×10^{-9} and 0·42 $sec.^{-1}$, respectively. Towards phosphorus, hydroxide ion is, therefore a better nucleophile than water by a factor of *ca.* 10^8. For attack on a saturated carbon atom the corresponding factor is much smaller, *i.e.*, *ca.* 10^4. Consequently, in a trisubstituted phosphate ester in which both carbon and phosphorus centres are open to substitution, hydroxide ion and water will tend to be selective for phosphorus and carbon, respectively.

Consistently with the above, trimethyl phosphate in the absence of hydroxide ions hydrolyses with carbon–oxygen bond fission. The reaction rate, in water, is not appreciably increased by the presence of up to 3M-perchloric acid; the reactive species is, therefore, the neutral molecule. The reaction presumably proceeds *via* an S_N2-type displacement on carbon, and analogous processes have been observed in methyl and dimethyl phosphate: [13,10]



$$H_2\ddot{O}\ \ \overset{H\ \ H}{\underset{H}{C}}{-}OPO(OMe)_2 \longrightarrow H_2\overset{+}{O}Me + {}^{-}OPO(OMe)_2 \quad . \ . \ . \ . \ . \ . \ . \quad (4)$$

The rates at 100° and in order of increasing methyl substitution are 0·5, 3·3, and $36{\cdot}5 \times 10^{-6}$ $sec.^{-1}$. After allowance for the statistical factor, the relative rates are 1·0, 3·3, and 24. The reaction is, therefore, favoured by increasing methyl substitution. The effect may, as discussed elsewhere,[8] be explicable in terms of the stability of the displaced anion.

Trimethyl phosphate shows no acid-catalysed hydrolysis in water as solvent. The rates of the acid-catalysed hydrolyses of methyl and dimethyl phosphate are approximately the same, *i.e.*, *ca.* $0{\cdot}13 \times 10^{-4}$ $sec.^{-1}$ at 100° with 3M-perchloric acid. If the rate for trimethyl phosphate has the same value, then the reaction would not be observed in water since it would be masked by the faster neutral reaction (*ca.* $0{\cdot}4 \times 10^{-4}$ $sec.^{-1}$ under the above conditions). Consistently, Thain [20] has shown that in dioxan–water (1 : 1 v/v),

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* The solvolysis of triphenyl phosphate has not been shown to proceed with phosphorus–oxygen bond fission, but this can, for structural reasons, be assumed.

[18] Holmann, *Bull. Res. Council Israel*, 1958, **7***A*, 106.

[19] Cox, Wall, and Westheimer, *Chem. and Ind.*, 1959, 929.

[20] Thain, *J.*, 1957, 4694.

in which the rate of the neutral reaction is much reduced, acid-catalysed hydrolysis of trimethyl phosphate may be observed.

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